

## **REMARKS**

### **I. Finality of Rejection and Request for Continued Examination (RCE)**

Upon receipt of the final Office Action, the Applicants telephoned the Examiner on April 16, 2004 and May 6, 2004 requesting reconsideration of the finality of the rejection. The Examiner reaffirmed her position that the finality of the rejection was proper. Therefore, the Applicants filed a petition on June 8, 2004 to withdraw finality as premature. Despite numerous telephone inquiries, the Applicants are still awaiting a decision regarding the petition. If the Applicants' petition is granted, then the Applicants request that the Patent and Trademark Office treat this submission as a response to a non-final action and refund the Applicants' fee for filing of an RCE.

### **II. Amendments**

Claims 7-24 and 31 stand rejected and are currently being examined. Claims 7-12, 14-18, and 20-24 are amended herein. Thus, claims 7-24 and 31 are currently pending.

Claim 7 is amended to remove reference to "a species homolog thereof," a term to which the Examiner has objected. Support for the amendment to claim 7 can be found throughout the specification and at least at page 14, lines 5-19, and page 19, lines 3-32.

Claims 8, 9, 12, 14, 15, 18, 20, 21, and 24 are amended to replace "atpG gene product" with "atpG polypeptide." Support for this amendment can be found throughout the specification and at least at page 7, lines 6-11 and 22-23 and page 14, lines 13-19.

Claims 10, 11, 12, 16, 17, 18, 22, and 23 are amended to replace "atpG gene" with "nucleotide sequence that encodes an atpG polypeptide." Support for this amendment can be found throughout the specification and at least at page 7, lines 6-11 and 22-23 and page 14, lines 13-19.

Claims 11, 17, and 23 are amended to remove redundancy in the recitation of the percentages of the nucleotide sequence, resulting from a mutation that will be tolerated in the claimed bacteria. Support for this amendment can be found throughout the specification and at least at page 5, lines 27-31 and page 12, lines 2-7.

The Applicants do not intend by any amendments to abandon the subject matter of any claim previously presented. The Applicants reserve the right to pursue the

subject matter of such claims during prosecution of this or subsequent applications. The amendment includes no new matter.

### **III. Patentability Arguments**

Reconsideration and withdrawal of the rejections is solicited for the reasons set out below. This response is timely filed as it is accompanied by a petition for an extension of time and the requisite fee.

#### **A. The Anticipation Rejection of Claim 7 under 35 U.S.C. § 102(b), May Properly Be Withdrawn.**

The Examiner rejected claim 7 under 35 U.S.C. § 102(b) for anticipation by Gwinn et al., *J. Bacteriol.* 179:7315-7320, 1997 (hereinafter “Gwinn”), because Gwinn assertedly discloses the instantly claimed invention directed to isolated mutant strains of *Haemophilus influenzae* ( a member of the *Pasteurellaceae* family), the mutant strains comprising a mutation in an atpG species homolog, specifically atpA or atpB gene, wherein the strain was attenuated through reduced expression of induced competence genes. The Applicants respectfully traverse the rejection.

In claim 7, as amended, the Applicants are claiming an attenuated *Pasteurellaceae* bacteria comprising a mutation in the nucleotide sequence that encodes an **atpG** polypeptide, i.e., the ATP synthase F1 gamma chain (atpG) polypeptide. Gwinn discloses mutant strains of **atpA** and **atpB** of *Haemophilus influenzae*, which are completely different genes/polypeptides and exhibit completely different activities than atpG. The Applicants are claiming attenuated *Pasteurellaceae* bacteria comprising mutations in the nucleotide sequence that encodes an **atpG** polypeptide, not comprising mutations in the nucleotide sequences that encode atpA or atpB polypeptides.

For these reasons, the rejection of claim 7 under 35 U.S.C. §102(b) for anticipation by Gwinn is now rendered moot and should be withdrawn.

**B. The Written Description Rejection of Claims 7-24 and 31 under 35 U.S.C. §112, First Paragraph, May Properly Be Withdrawn.**

The rejection of claims 7-24 and 31 under 35 U.S.C. §112, first paragraph, is maintained for assertedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor, at the time the application was filed, had possession of the invention. The Office Action at page 3 asserts that what is now claimed is not limited to mutations within the open reading frame that encodes “the gamma subunit of ATPase” set forth in SEQ ID NO: 3, but is directed to mutant genes that comprise the coding sequences for gamma subunits of ATPase from any gram negative bacteria, to include functional homologs that have a similar activity, not requiring the same activity, which reads on other ATPase subunits (such as atpH) as well as mutations in regulatory regions that modulate transcription of the virulence gene and is therefore not limited to mutations within the coding sequence for the gamma subunit of ATPase of SEQ ID NO: 3, or open reading frames that encode gamma subunits of ATPase. The Applicants respectfully disagree.

Claim 7, as amended, recites “comprising a mutation in the nucleotide sequence that encodes an atpG polypeptide.” Thus, the mutation is in the protein coding region of the nucleotide that encodes the atpG polypeptide, because the protein coding region of a gene is within the open reading frame. Claim 7 also recites that said mutation “results in decreased atpG biological activity.” Thus, the Examiner’s rejection, as it pertains to attenuated bacteria comprising homologs not requiring the same activity as atpG, is unfounded. The claim specifies both that the mutation is in the nucleotide sequence that encodes an atpG polypeptide, and it results in decreased atpG biological activity.

The Office Action at pages 4-7 provides a litany of references which infer that knowledge of atpG gene placement on a bacterial chromosome is essential to having possession of the claimed invention, and asserts that the Applicants did not have possession of the genetically highly variable genus of *Pasteurellaceae* bacteria. The Applicants respectfully disagree.

The location of the atpG gene within the bacterial genome and the genetic variability of *Pasteurellaceae* is irrelevant to the claimed invention because a person of ordinary skill can locate it and alter it. The specification provides two working examples of attenuated *Pasteurellaceae* bacteria, *Pasteurella multocida* and *Actinobacillus pleuropneumoniae*, comprising mutations in the open reading frame of the atpG gene (SEQ

ID NO: 3 in *Pasteurella multocida* and SEQ ID NO: 132 in *Actinobacillus pleuropneumoniae*), which demonstrated decreased virulence in animals. In addition, the specification provides the identification of atpG genes by Southern hybridization in several species of the claimed genus of *Pasteurellaceae* bacteria, e.g., *Pasteurella haemolytica*, *Pasteurella multocida*, *Actinobacillus pleuropneumoniae*, and *Haemophilus somnus*. One of skill in the art can readily isolate and sequence atpG genes from bacterial species that can be identified and mapped using Southern hybridization and related techniques, and target said genes using site-directed mutagenesis or other methods. The use of a sequence similarity limitation (at least 70% identity) harmonizes with the ability to identify other atpG genes by hybridization because hybridization occurs between similar (complementary) sequences. Thus, the invention involves the identification of the atpG gene as being important to bacterial virulence, and shows that the disruption of the atpG gene attenuates the *Pasteurellaceae* bacteria. The hybridization experiment shows that the Applicants were in possession of the claimed invention, currently defined in part by sequence similarity to sequences provided in the application. There is ample precedent for defining a genus by sequence similarity. The Applicants should be permitted to claim as broadly as the art allows and the specification describes and enables. The Applicants have demonstrated that *Pasteurellaceae* bacteria with disruptions in the open reading frame of the atpG gene are attenuated and are capable of providing protective immunity against wild-type bacteria of the same strain. The claims are directed, e.g., to an attenuated bacteria comprising an atpG mutation. As demonstrated by the Examples, it is not necessary to know the sequence of an atpG homolog to make and use the claimed invention. It was not necessary to know the complete sequence of the *Pasteurella multocida* atpG gene to construct the mutant in Example 1 or to demonstrate that the mutant is attenuated in Example 2. This is true of other *Pasteurellaceae* family members as demonstrated in *Actinobacillus pleuropneumoniae* in Example 5 and there is nothing of record to suggest that this would not be true for any *Pasteurellaceae* family members.

As Applicants discussed in their previous response, the claims are not drawn to polynucleotides but rather, an organism (bacteria) comprising a genetic modification at a particular locus (gene), providing a specified change of phenotype. The Applicants have described the organism, the gene, the type of change to make, and the phenotype (attenuated) to select. The Applicants do not need to specifically point out where the mutation is located in the sequence. Indeed, in claims to more complicated transgenic animals comprising a

"knockout" of a particular endogenous gene, the Patent Office does not require that claims be limited to the specific disruption or SEQ ID NO. disclosed, see e.g., U.S. Patent Nos. 5,714,667; 5,777,195; 6,087,555; and 6,100,445. The presently claimed attenuated bacteria are analogous to knockout animals having a particular phenotype. The rejection does not put forth any reasoning as to why a claim directed to a bacteria lacking expression of a particular gene must distinctly claim the particular sequence of the mutation, whereas a claim directed to an animal lacking expression of a particular gene does not. In this regard, it is worth noting that bacteria contain a genome that is orders of magnitude smaller and organized much simpler than, e.g., transgenic mice. Accordingly, the written description requirements for bacteria should not be more stringent.

Because the examiner has failed to provide reasoning or evidence to support the rejection, except to cite art which is not relevant to the invention being claimed; because the Applicants have provided working examples of the claimed genus of bacteria in the specification; and because of amendments to the claims, the Applicants respectfully request reconsideration and withdrawal of the rejection of claims 7-24 and 31 under 35 U.S.C. §112, first paragraph, for lack of written description.

**C. The Indefiniteness Rejections of Claims 7-24 and 31 under 35 U.S.C. §112, Second Paragraph, May Properly Be Withdrawn.**

The Examiner maintains the rejection of claims 7-24 and 31 under 35 U.S.C. §112, second paragraph, as assertedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention for reciting mutations in homolog genes and gene products, and activity of the homolog gene products, which are not clearly set forth in the claims. The Applicants respectfully disagree and submit that the claims, as originally filed, are not indefinite.

This rejection is now moot, however, in view of the amendments to claims 7-12, 14-18, and 20-24 which recite a combination of structural and/or functional characteristics for the genes and polypeptides that are described and enabled in the specification, and remove references to the terms "gene", "gene products", and "homologs". The bacterial genus of claim 7, as amended, all comprise a mutated atpG polynucleotide, wherein its mutation results in decreased atpG activity, which results in attenuation of the *Pasteurellaceae* bacteria. Therefore, the combination of structural and functional activity for

atpG, provided in the claims as amended, allow one of skill in the art to clearly delineate other species of atpG not known in the art. Support in the specification for atpG biological activity is found in Example 10. The specification describes how atpG functions in ATP synthase, e.g., by the production of ATP or in the transport of protons by hydrolyzing ATP. Given the base sequence information of the atpG polypeptide in *P. multocida* (e.g., SEQ ID NO: 4), the specifically identified activity of atpG, and the well-known techniques for isolating atpG genes from a variety of *Pasteurellaceae* bacteria species (see Example 5), the Applicants submit that one skilled in the art clearly would be able to identify other bacteria within the scope of the claimed invention.

The Applicants also maintain their position that they do not need to specifically point out where the mutation is located within the atpG sequence, as long as the mutation disrupts the expression and function of the encoded atpG polypeptide. Indeed, in claims to transgenic animals comprising a "knockout" of a particular endogenous gene, the claims are not limited to the specific site of disruption within the sequence or SEQ ID NO. disclosed, see e.g., U.S. Patent Nos.: 5,714,667; 5,777,195; 6,087,555; and 6,100,445. The presently claimed attenuated bacteria are analogous to knockout animals having a particular phenotype because the patents at issue do not describe the sequence of every homolog of the gene of every mouse within the scope of the issued claims. The rejection does not put forth any reasoning as to why, for purposes of definiteness, a claim directed to a bacteria lacking expression of a particular gene must claim the mutation with the level of specificity suggested by the Examiner, whereas a claim directed to an animal lacking expression of a particular gene does not. The claimed genus of attenuated bacteria, as presently amended, recite a combination of functional (atpG activity) and structural (polypeptide comprising an amino acid sequence at least 70% identical to the atpG amino acid sequence of SEQ ID NO:4) properties which are definite. The claimed bacteria comprise a mutation in a polynucleotide encoding atpG, which results in the disrupted function of atpG activity, resulting in attenuation. One of skill in the art should clearly be able to identify the scope of the claimed invention.

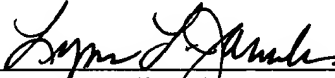
For these reasons, the rejection of claims 7-24 and 31 under 35 U.S.C. §112, second paragraph, for indefiniteness is now rendered moot and should be withdrawn.

#### IV. Conclusion

In view of the amendments and remarks made herein, Applicants respectfully submit that claims 7-24 and 31 are in condition for allowance and respectfully request expedited notification of same. Should the Examiner have any questions of form or substance, she is welcomed to contact the undersigned at the telephone number below.

Respectfully submitted,

MARSHALL, GERSTEIN & BORUN  
6300 Sears Tower  
233 South Wacker Drive  
Chicago, Illinois 60606-6357  
(312) 474-6300

By: 

Lynn L. Janulis, Ph.D.

Registration No. 53,066

October 8, 2004